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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,507	03/12/2004	Young-Choon Moon	2004993-0043 (VPI/03-01)	8237

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/799,507	MOON, YOUNG-CHOON	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 16-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6-8,12,21 and 22* is/are allowed.

6)☒ Claim(s) *1,2,4,5,9-11 and 16-20* is/are rejected.

7)☒ Claim(s) *3* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01182005*. (1 Page)
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on March 17, 2005.

Claims 1-12 and 15-22 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 16-17 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of stroke, does not reasonably provide enablement for a method of inhibiting the activity of various receptors recited in the claims or treating or lessening severity of diseases or conditions recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Note: *Claim 19 was not treated on the merits in the previous office action due to its improper form.*

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant first argues that 'the connection between GSK-3 and the diseases set forth in claims 16 and 17 was well established at the time of filing'. Applicant relies on the state of

the art reference of record (Hardt) and argues that the claims are enabled for the diseases recited in the claims. However, the reference clearly indicates the unpredictability of the role of GSK-3 inhibitors in the treatment of diseases, e.g., cardiac hypertrophy. The reference does not provide sufficient guidance in the form of administration profiles, combination ratios of the active agents or references to same in the prior art and therefore enable the skilled artisan with sufficient guidance to practice the instant therapeutic methods. The arguments presented by the applicant are drawn to specific diseases and not to the generic groups of diseases recited in the claims, e.g., a cardiac disorder, a neurodegenerative disorder, etc. many of which embrace multitude of diverse disease conditions that are extremely difficult to treat.

Applicant cites Aricept® as a drug approved by FDA for the treatment of Alzheimer's disease. However, ARICEPT® (donepezil hydrochloride) is a reversible inhibitor of the enzyme acetylcholinesterase as compared to the GSK-3 inhibitor activity disclosed for the instant compounds. Further, applicants have not provided how this links to the entire range of neurodegenerative diseases, which are known to be very difficult even to classify. Contrary to applicant's arguments, Hardt reference does not provide correlation between all types of diseases of the instant claims. While the reference indicates that 'GSK-3β regulates a wide range of cellular functions', the reference clearly expresses 'the many unanswered questions such as the other functions of GSK-3 β in the heart', etc. Therefore, it is maintained that applicant has not provided sufficient evidence to meet the enablement requirements of the instant claims reciting method treating assorted diseases or disorders having diverse mechanisms and etiologies.

Applicant cites *In re Brana* and argues that 'only a *reasonable correlation* is required, and the test data does not have to be *highly predictive*'. Applicant's reliance on the *Brana*

decision is erroneous since the facts were different in more than one respect from the instant case. Compounds on appeal were of a much narrower scope and there were no method claims. Said compounds were similar in structure to compounds displaying *in vivo* anti-tumor activity based on art-recognized *in vivo* tests and also tested favorably in an *in vivo* test. Thus, contrary to *Brana* it is not evident that at the time of applicant's effective filing, the compounds of formula I having such a diversity of substituents are well known for 'treating the wide range of diseases generally' urged treatable based simply on test assays relied on herein.

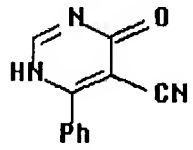
While the specification provides sufficient enabling disclosure for the synthesis of the instantly claimed compounds, does not provide an enabling disclosure sufficient to cover the entire scope of the methods of use recited in the instant claims. The instant claims include 'treatment of several types of diseases having diverse mechanisms - affecting different organs and having different methods of growth or harm to the body, and different vulnerabilities'.

The state of the art does not identify a single class of compounds that can treat all types of diseases of the instant claims. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to

construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the method of inhibition or treatment commensurate in scope with the claims, as of the filing date of the application.

2. Claims 1-2, 4-5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Mittelbach et al., CAPLUS Abstract 92:146395. The instant claims read on reference disclosed compound, see the compound disclosed in the abstract (depicted below for convenience).

CN 5-Pyrimidinecarbonitrile, 1,4-dihydro-4-oxo-6-phenyl- (9CI)



Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant relies on 'the amendments to claim 1 as described in page 33' to overcome the rejection (see the last paragraph in page 33). The compounds according to claim 1 as amended do not include $-OR^1$ as a substituent on ring A, which is not sufficient to remove the reference compound. Claim 1 also recites the limitation – "provided that when ring A is phenyl, it must be substituted", however, ring A optional substituent list includes R^1 which is defined as hydrogen.

The following rejections are under new grounds:

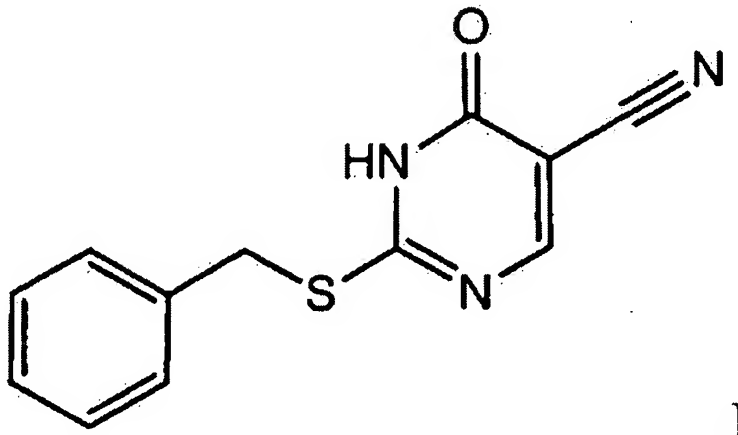
Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9 and 19 recite the limitation " compound I-9" (depicted below for convenience) (see claim 9, page 6, line 1 and claim 19, page 19, line 3). There is insufficient antecedent basis for this limitation in claim 1 or claims 16-18 on which these claims are respectively dependent.



I-9

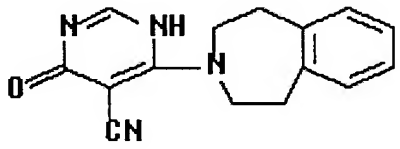
The generic structural formula disclosed in the specification, the Schemes I and II disclosed for the preparation of the compounds of the invention do not support the above structural formula.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-5, 10-11, 16-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Adam et al., EP 1074549. The instant claims read on reference disclosed compound, see the structural formula I in page 2 and the species of Example 15 (depicted below for convenience):



According to the instant claims, ring A is an aryl ring which is optionally substituted by 1-4 substituents wherein two substituents taken together with the atoms to which they are attached may form a 3-8 membered ring. The reference teaches that the compounds are useful in the treatment of stroke, Alzheimer's disease, parkinsonism, etc., see page 4.

Allowable Subject Matter

Claims 6-8, 12 and 21-22 are allowed. The references of record do not teach or fairly suggest the instantly claimed compounds. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Receipt is acknowledged of the Information Disclosure Statement filed on January 18, 2005 and a copy is enclosed herewith. The International Search Report for International Application PCT/US2004/007801 is also acknowledged and all the cited documents have been fully considered. The citation of the search report was removed from PTO 1449 (by drawing a line through) because the "International Search Report" itself is not a proper publication *per se* that complies with the requirements of 37 CFR 1.97 and 1.98 and therefore, will not appear on the patent as a cited document.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

June 10, 2005